

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-061 and 21-062

ADMINISTRATIVE DOCUMENTS

PATENT INFORMATION

Patent No.: 4,980,470
Expiration Date: December 25, 2007
Type of Patent: Drug
Patent Owner: Kyorin Pharmaceutical Co., Ltd.

Bristol-Myers Squibb Company is the exclusive licensee of U.S. Patent No. 4,980,470.

DECLARATION

The undersigned declares that U.S. Patent No. 4,980,470 covers the drug substance for which approval is being sought in this NDA.

David M. Morse
Signature of authorized person

David M. Morse
Name of authorized person

Patent Counsel - Wallingford
Title of authorized person

September 16, 1998
Date

Exclusivity Checklist

NDA: 21-061, 21-062			
Trade Name: Tequin			
Generic Name: Gatifloxacin			
Applicant Name: Bristol Myers Squibb Corporation			
Division: Division of Special Pathogen and Immunologic Drug Products			
Project Manager: Brenda Atkins/Laurie Bernato			
Approval Date: December 17, 1999			
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?			
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.			
a. Is it an original NDA?	Yes	<input checked="" type="checkbox"/>	No
b. Is it an effectiveness supplement?	Yes		No <input checked="" type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")			
Yes	<input checked="" type="checkbox"/>	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.			
Explanation:			
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:			
Explanation:			
d. Did the applicant request exclusivity?	Yes	<input checked="" type="checkbox"/>	No
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?		five years	
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.			
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?			
Yes		No	<input checked="" type="checkbox"/>
If yes, NDA #			
Drug Name:			
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE			

BLOCKS.

3. Is this drug product or indication a DESI upgrade? ☐ Yes ☒ No ☐ x

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product. ☐ Yes ☒ No ☐ x

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

Yes No x

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product

NDA #

Drug Product

NDA #

Drug Product

NDA #

2. Combination product. ☐ Yes ☐ No ☒ x

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

Yes No x

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product

NDA #

Drug Product

NDA #

Drug Product

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY

TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	No		
--	-----	----	--	--

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	No		
--	-----	----	--	--

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes	No		
---	-----	----	--	--

1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes	No		
--	-----	----	--	--

If yes, explain:

2) If the answer to 2 b) is "no," are you aware of published				
--	--	--	--	--

studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes	No
If yes, explain:		
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:		
Investigation #1, Study #:		
Investigation #2, Study #:		
Investigation #3, Study #:		
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.		
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")		
Investigation #1	Yes	No
Investigation #2	Yes	No
Investigation #3	Yes	No
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:		
Investigation #1 -- NDA Number		
Investigation #2 -- NDA Number		
Investigation #3 -- NDA Number		
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?		
Investigation #1	Yes	No
Investigation #2	Yes	No
Investigation #3	Yes	No
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:		
Investigation #1 -- NDA Number		
Investigation #2 -- NDA Number		
Investigation #3 -- NDA Number		
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):		
Investigation #1		
Investigation #2		

Investigation #3			
<p>4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.</p>			
<p>a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?</p>			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			
<p>b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?</p>			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			
<p>c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may</p>			

not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes	No
If yes, explain:		



Signature of PM/CSO

Date: 1/19/00

IS/

Signature of Division Director

Date: 4/19/00

IS/

cc:

Original NDA

Division File

HFD-93 Mary Ann Holovac



PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21061</u>	Trade Name:	<u>TEQUIN (GATIFLOXACIN) 200/400MG TABS</u>
Supplement Number:		Generic Name:	<u>GATIFLOXACIN</u>
Supplement Type:		Dosage Form:	<u>TAB</u>
Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>Acute sinusities uncomplicated UTI complicated UTI CAP gonorrhea chronic bronchitis sinusitis</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

☐ NeoNates (0-30 Days) ☐ Children (25 Months-12 years)
☐ Infants (1-24 Months) ☐ Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO**COMMENTS:**

Uncomplicated skin and skin structure infections indication is approvable. FDA is waiving the pediatric study requirement for this action on this application.

The submission of the four month safety update (Amendment No. 12, submission date 5 May 1999), the applicant indicated that they have begun clinical studies in the pediatric population.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
DOLORES BERNATO

Signature

Date

CERTIFICATION: DEBARRED PERSONS

As required by Section 306 (k) (1) of the Food Drug and Cosmetic Act, Bristol-Myers Squibb hereby certifies that it did not and will not use in any capacity the services of any person disbarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this Application.



12/22/98
Date

Douglas C. Kriesel, Ph.D.
Director, Worldwide Regulatory Affairs
Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492
(203) 677-6883

CLAIM OF CATEGORICAL EXCLUSION

The subject NDAs (No. 21-061 and No. 21-062) qualify for categorical exclusion under 21 CFR 25.31(b). Further, to our knowledge, no extraordinary circumstances exist necessitating the submission of an Environmental Assessment (EA) in support of this application.

MEETING MINUTES

MEETING DATE: December 6, 1999 **TIME:** 11 AM **LOCATION:** Corp S400

HFD-590- Division of Special Pathogen and Immunologic Drugs

NDAs- 21-061, 21-062

DRUG: Gatifloxacin- Tequin™

Proposed Indications:

1. Acute sinusitis (AS)
2. Uncomplicated urinary tract infections (UTI)
3. Complicated urinary tract infections including pyelonephritis
4. Community acquired pneumonia (CAP)
5. Acute exacerbations of chronic bronchitis (AECB)
6. Uncomplicated skin and skin structure infections (USSSI)
7. Uncomplicated urethral, pharyngeal, and rectal gonorrhea in males, and uncomplicated endocervical, pharyngeal, and rectal gonorrhea in females (UG)

SPONSOR/APPLICANT: Bristol -Myers Squibb

TYPE of MEETING: Pre-Approval Safety Conference

REVIEW DIVISION PARTICIPANTS:

D. Laurie Bernato, R.N., MN, Regulatory Project Manager
Renata Albrecht, M.D., Acting Dep.Dir, ODE IV
Thomas Hassall, RPh., Assistant Director for Regulatory Affairs
Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader
Joyce Korvick, M.D., MPH, Project Team Leader
Rosemary Tiernan, M.D., Medical Officer
Rigoberto Roca, M.D., Medical Officer
Karin Higgins, Ph.D., Statistical Reviewer
Kathleen Uhl, M.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Peter Dionne, M.S., Microbiology Reviewer
Amy Ellis, Ph.D., Pharmacologist
Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Ziad Akl, M.D., Medical Officer
Lisa Hubbard, R.Ph., Regulatory Project Manager
Brad Leissa, M.D., Medical Team Leader

OPDRA PARTICIPANTS:

Evelyn Rodriguez, M.D., MPH, Division Director, DDRE II

December 6, 1999

Toni Piazza-Hepp, Pharm.D. TL, Safety Evaluator
Sarah Singer, R.Ph., Safety Evaluator
Mary Dempsey, Project Manager

DDMAC PARTICIPANTS:
None

MEETING OBJECTIVES:

To provide a routine, formal mechanism for communications between the Office of Drug Evaluation (ODE) review divisions and the Office of Post-Marketing Drug Risk Assessment (OPDRA) risk evaluation divisions prior to the approval of a new chemical entity (NCE) or certain other applications in order to:

- (1) Ensure that OPDRA is aware of potential post-marketing safety problems of drugs about to be approved,
- (2) Consider, jointly, the need for any special post-marketing analyses or post-marketing safety studies or other evaluations to be implemented by or agreed to by the sponsor prior to the approval of a drug product, and
- (3) Determine if there were any special information or feedback that the ODE review division would like from the OPDRA risk evaluation division during the immediate post-launch life of the soon-to-be-approved drug product.

The safety database indicates that the most frequently seen adverse events among patients treated with gatifloxacin include headache, nausea, vaginitis, and drowsiness. The applicant reported integrated adverse clinical events according to the gatifloxacin dose administered, with the 400 mg PO dose being the one most frequently administered. Most of the adverse clinical events in the 400 mg group, were reported to be of mild to moderate severity. The most common reasons for the discontinuation of were diarrhea and vomiting.

The major safety concern is the potential to prolong the QTc of the electrocardiogram in some patients. Studies concerning the effects of gatifloxacin on the QTc will be part of the Phase IV commitments.

ACTION ITEMS: (Include description, identify person responsible and due date.)

1. QT interval issues will be monitored by OPDRA.

December 6, 1999

2. OPDRA will do an epidemiology review on the active surveillance study when it is submitted by BMS.

Concurrence: Co-Chair: Evelyn M. Rodriguez, MD, Dir. DDMAC - electronically 02/17/00
Co-Chair: Renata Albrecht, MD, Dep. Div. Dir. /S/

Date: 2/22/2000

Minutes preparer-Regulatory Project Manager /S/

Date: 2/23/2000

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Medical Team Leader's Memorandum

TO: NDAs 21-061 and 21-062

FROM: Marc Cavaillé-Coll, M.D., Ph.D.

/S/
12/10/99 NDA 21-062

RE: Tequin®(gatifloxacin) Tablets, NDA 21-061
and Tequin® IV, NDA 21-062

DATE: December 10, 1999

GENERAL

The original NDAs for Tequin®(gatifloxacin) Tablets, NDA 21-061 and for Tequin® IV, NDA 21-062, were submitted December 28, 1998. The applicant, Bristol-Myers Squibb Company, has requested approval for seven different indications:

- Community acquired pneumonia (CAP)
- Acute exacerbations of chronic bronchitis (AECB)
- Uncomplicated skin and skin structure infections (USSSI)
- Uncomplicated urethral, pharyngeal, and rectal gonorrhea in males, and uncomplicated endocervical, pharyngeal, and rectal gonorrhea in females (UG)
- Acute sinusitis (AS)
- Uncomplicated urinary tract infections (UTI)
- Complicated urinary tract infections including pyelonephritis (UTI)

The review of these indications was divided among several reviewers. Dr. Joyce Korvick, the Lead Medical Reviewer for this application, performed the review of CAP, the Integrated Review of Safety and coordinated the clinical reviews with the assistance of the Project Manager for this product, Ms. Brenda Atkins.

Review of this very bulky submission was facilitated by the electronic submission of data files, case report forms and study reports. The applicant submitted data files in SAS-transport format which could be used with the JMP program recommended by Center's existing Guidance on Electronic Submissions (www.fda.gov/cder/guidances/index.htm). Case report forms and patient profiles for all patients enrolled in the trials were submitted in PDF format. Study reports for the trials were submitted as MS-Word documents. This was the first large application in this division to use JMP analysis of the electronic data on such a scale.

This presented an opportunity to evaluate the performance of JMP in assisting a thorough clinical review. Several difficulties that might be improved upon were identified and described in some of the individual reviews. In particular, this program did not have a feature where tables of summary results could be readily imported into a wordprocessing

document. Thus, a fair amount of time was spent by reviewers transferring information from JMP to wordprocessing.

The remainder of this memo will address particular aspects of the approved indications, the approvable indications, the withdrawn indications, safety considerations, risk management considerations, waiver of requirement for pediatric studies, and the phase 4 commitments.

APPROVED INDICATIONS

The applicant has requested several indications for which other antibiotic therapies, including penicillins and cephalosporins, exist. As a class, the fluoroquinolones possess a different mechanism of action than the beta-lactam antibiotics, and are expected not to share overlapping mechanisms of resistance with them. Gatifloxacin, like newer members of its class, also possesses activity against some of the important Gram-positive bacteria in addition to activity against Gram-negative organisms. The single daily dosing regimens should also enhance compliance with completion of the full treatment regimens for each indication. These considerations in addition to the evidence of effectiveness, summarized in this memorandum, favor approval of gatifloxacin for the indications below.

Approval of gatifloxacin for these indications is also based on a favorable risk benefit assessment, which should be enhanced by wording in the WARNINGS and PRECAUTIONS sections of the approved label, and by inclusion of a patient information section (See SAFETY CONSIDERATIONS and RISK MANAGEMENT below).

Community Acquired Pneumonia (CAP)

The clinical data for this indication were derived from five clinical studies, including two uncontrolled studies and three randomized, double-blind, multicenter studies comparing gatifloxacin to clarithromycin, ceftriaxone and levofloxacin, respectively. These studies included mild, moderate and severe cases of CAP. The clinical cure rates for gatifloxacin, in the evaluable patient population ranged from 88% to 90%, compared to 85% to 93% in the comparator population. Overall, the lower limits of the 95% confidence intervals of the difference in cure rates (gatifloxacin rate – comparator rate) did not exceed –15%, the lower limit used to define equivalence based on an estimated cure rate of 80% in the prospective data analysis plan. The highest cure rates were observed in the study comparing gatifloxacin to levofloxacin, 90% and 93%, respectively. In this study the 95% confidence interval of the difference in cure rates among clinically evaluable patients was -11.5% to 3.6%, which included zero, but exceeds –10%. However, the high cure rates in this study mitigate concerns that gatifloxacin might not be at least as effective as levofloxacin in this indication. Overall, this data and the analyses from the other controlled studies, provide substantial evidence that gatifloxacin is effective in this indication, using oral therapy or intravenous-to-oral switch therapy.

From a bacteriological point of view, gatifloxacin demonstrated adequate activity against the principal pathogens involved in CAP (*S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis* and *S. aureus*). However, while eradication rates were high for *K. pneumoniae* and penicillin resistant *S. pneumoniae*, there were not enough clinical isolates to reliably support efficacy against these organisms.

Data was also presented on presumed eradication of atypical pathogens in a small number of subjects with atypical pneumonia due to *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. This information supports the inclusion of these pathogens in the approved label.

I concur with the reviewers' recommendation that gatifloxacin (Tequin™), 400 mg PO, or IV switched to PO, qd for 7 to 14 days, be approved for the treatment of community acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible only), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*.

Acute Exacerbation of Chronic Bronchitis (AECB)

Overall the clinical data are not very robust and should be interpreted in light of the efficacy demonstrated in the indication of community acquired pneumonia (CAP). In particular, gatifloxacin showed a somewhat lower efficacy rate compared to levofloxacin but was at least as good as cefuroxime. From a bacteriological point of view, gatifloxacin demonstrated adequate activity against the principal pathogens involved in AECB (*H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *S. aureus*, and *H. parainfluenzae*). However, while eradication rates were high for *K. pneumoniae*, *E. cloacae* and penicillin resistant *S. pneumoniae*, there were not enough clinical isolates to reliably support efficacy against these organisms.

Because it was expected that smoking status might influence study outcome, this variable was taken into consideration in the randomization of the two controlled studies. A notable finding in the two controlled studies was that patients who were classified at study entry as current non-smokers, based on not having smoked for the past 2 months, had a lower cure rate than current smokers. Exploratory logistic regression analyses, requested from the applicant, did not identify factors or combination of factors that might completely explain this observation. Nevertheless, the prognostic importance of this variable should be interpreted with caution.

Because of the supportive data in CAP, I concur with the reviewers' recommendation that gatifloxacin (Tequin™), 400 mg PO qd for 7 to 10 days, be approved for the treatment of acute exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, and *Staphylococcus aureus*.

Uncomplicated Gonorrhea

The clinical data for this indication were derived from a single, large double-blind, active control trial conducted at 13 centers in the United States. Gatifloxacin was 99% effective at 400mg PO and 600mg PO in eradicating gonorrhea from the urethra in men and the cervix in women. Adequate numbers of both men and women were studied to support the indications. In addition, there were adequate data to support approval of treatment of rectal gonorrhea in women; however, there are no data on the treatment of rectal gonorrhea in men. The information on pharyngeal gonorrhea treated with 400 mg PO, the proposed dosing regimen, was found to be marginal for both males and females.

Overall, I concur with the reviewer's recommendation that gatifloxacin, a single 400mg oral dose, be approved for the treatment of uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae*, and acute uncomplicated rectal infections in women due to *Neisseria gonorrhoeae*. The package insert should also note that efficacy of gatifloxacin in treating male patients with rectal infections and male or female patients with pharyngeal infections caused by *N. gonorrhoeae* has not been established. Note that because of the advantages of a single dose regimen and the limited exposure to gatifloxacin, when using a such a regimen, the limited risks of a potential QTc effect are adequately outweighed by the potential clinical benefits (See SAFETY CONSIDERATIONS and RSIK MANAGEMENT below).

Acute Sinusitis

The clinical data for this indication was derived from three clinical studies, including two controlled studies that compared gatifloxacin to clarithromycin and trovafloxacin, respectively, and one open-label uncontrolled study. As noted in Dr. Mann's review, the results in the first controlled study were only marginally supportive of gatifloxacin's equivalence to the approved comparator agent clarithromycin. There developed a need for additional information to support the efficacy of gatifloxacin in this indication. Thus, the second controlled study was submitted as a major clinical amendment to the NDA on June 11, 1999. In this study the efficacy rates were higher and gatifloxacin was clearly shown to meet the protocol-specified criteria for equivalence to the approved comparator, trovafloxacin. Finally, the open-label uncontrolled study produced an efficacy rate similar to those seen in the controlled studies.

Acute sinusitis represents a significant infection with serious medical outcomes if not adequately treated. This must be taken into consideration in assessing the balance between potential risks and benefits associated with this drug. Overall, I concur with the reviewer's recommendation that gatifloxacin, 400 mg P.O. qd for 10 days, should be approved for the treatment of acute sinusitis due to *Streptococcus pneumoniae* and *Haemophilus influenzae*. Insufficient data were presented to support labeling of acute sinus infections due to *Moraxella catarrhalis* or penicillin-resistant strains of *Streptococcus pneumoniae*.

Complicated Urinary Tract Infection

The clinical data for this indication were derived from two randomized, double-blind clinical trials comparing gatifloxacin to ciprofloxacin. Analysis of the response rates among the microbiologically evaluable population support that gatifloxacin was equivalent to ciprofloxacin in patients with complicated UTI, including patients with pyelonephritis. From a bacteriological point of view, gatifloxacin demonstrated adequate activity against *E. coli*, *K. pneumoniae* and *P. mirabilis*. There were insufficient numbers of clinical isolates to support activity against *Enterococcus faecalis*, *Pseudomonas aeruginosa* or *Enterobacter spp.*

Complicated urinary tract infections also represent significant conditions with serious medical outcomes if not adequately treated. This must be taken into consideration in assessing the balance between potential risks and benefits associated with this drug. Overall, I concur with the reviewer's recommendation that gatifloxacin, 400 mg per day, for 7 to 10 days be approved for the treatment of complicated urinary tract infection due to *E. coli*, *K. pneumoniae* and *P. mirabilis* and pyelonephritis due to *E. coli*.

Uncomplicated Urinary Tract Infection

The clinical data for this indication were derived from a single randomized, double-blind clinical trial which compared two dosing regimens of gatifloxacin, a single oral dose of 400 mg, or 200 mg PO qd for three days, to Ciprofloxacin 100 mg PO bid for three days. Analysis of the response rates among the microbiologically evaluable population support that the two gatifloxacin regimens were equivalent to ciprofloxacin in the treatment of uncomplicated urinary tract infection. From a bacteriologic point of view, gatifloxacin demonstrated adequate activity against *E. coli*, *K. pneumoniae*, and *P. mirabilis*. There were insufficient numbers of clinical isolates to support activity against *Staphylococcus saprophyticus*.

This product would represent the first fluoroquinolone antibiotic to be approved for single dose usage in the treatment of this indication. A potential concern with a single dose regimen compared to a multi-dose regimen would be possible relapse with a resistant pathogen. In the microbiologically evaluable population, relapse rates (recurrence of the original pathogen) were similar between treatment groups. Among these small numbers of relapses, no isolates resistant to gatifloxacin were identified.

The potential risks of a rare but serious QTc effect are minimized by the limited drug exposure with the single dose or the three-day regimen at a lower dose (See SAFETY CONSIDERATIONS and RISK MANAGEMENT below). In addition, the inherent advantages of having an effective single dose regimen provide a favorable risk/benefit balance. The convenience of the single dose regimen or short, three single daily dose regimen, should enhance compliance with completion of the treatment.

Overall, I concur with the reviewer's recommendation that gatifloxacin 400 mg PO as a single dose or 200 mg PO qd for three days should be approved for the treatment of uncomplicated urinary tract infection due to *E. coli*, *K. pneumoniae* and *P. mirabilis*.

APPROVABLE INDICATIONS

While the clinical study summarized below have provided evidence of effectiveness in these indication, there are other treatment modalities for these infections that present a potentially lesser risk of serious adverse events in an otherwise healthy individual (See SAFETY CONSIDERATIONS and RISK MANAGEMENT below).

Uncomplicated Skin and Skin Structure Infections

The clinical data for this indication were derived from a single, large, double-blind, active-control multicenter trial conducted in the United States. Gatifloxacin was found to be as effective as the comparator, levofloxacin. There were sufficient numbers of simple abscesses, furuncles and cases of cellulitis, but insufficient numbers of impetiginous lesions. The latter are more common in children, a population that was excluded from this study (See SAFETY CONSIDERATIONS and WAIVER OF REQUIREMENT FOR PEDIATRIC STUDIES).

Overall, I concur with the medical reviewers' conclusions that gatifloxacin, 400 mg PO per day for 7 to 10 days, is effective in the treatment of uncomplicated skin and skin structure infections due to methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pyogenes*. If this indication were approved, the label should reflect the types of infections that were adequately represented in this clinical trial: simple abscesses, furuncles, folliculitis, wound infections and cellulitis. The label should also reflect that an insufficient number of patients with impetiginous lesions were available to evaluate the efficacy of gatifloxacin in this indication. Because of particular concerns over the effect of fluoroquinolones on the QTc interval, that were not fully addressed in this application, this indication should be considered approvable pending the sponsor's collection of more data to enable a risk/benefit determination to be made (Please see the applicant's Phase 4 commitments dated December 16, 1999).

WITHDRAWN REQUEST FOR APPROVAL OF PENICILLIN-RESISTANT *S. PNEUMONIAE* (PRSP)

In the original NDA submission on December 28, 1998, the applicant claimed that gatifloxacin was effective for the treatment of penicillin-resistant *S. pneumoniae* in patients with either acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis or community acquired pneumonia. In a facsimile transmission to the applicant on December 15, 1999, and during a subsequent telephone conference with the firm on December 16, 1999, the applicant was informed that adequate data to support this claim had not been provided. The applicant was informed that additional data documenting the clinical activity of gatifloxacin among patients with both penicillin-susceptible and penicillin-resistant *S. pneumoniae* should be submitted to support each of

these indications. Ideally, these should include efficacy data for patients with severe disease. In a subsequent letter, dated December 16, 1999, the applicant withdrew the request for approval of penicillin-resistant *S. pneumoniae* which appeared in the community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and acute sinusitis indications in the proposed package insert that had been provided in the original NDA submission.

SAFETY CONSIDERATIONS

When compared to drugs with no known potential for severe hepatotoxicity, based on extensive postmarketing experience, gatifloxacin did not demonstrate any significant increase in liver abnormalities.

Phototoxicity has been a concern with several antibiotics of the class of fluoroquinolones, and has seriously limited the use of some of these, including lomefloxacin and sparfloxacin. Based on structure-toxicity information, gatifloxacin would not be presumed to be associated with an increased risk in phototoxicity. Indeed, in the clinical database of more than 4000 patients treated with gatifloxacin no phototoxic events were reported by investigators. When evaluated in formal studies of phototoxicity in normal healthy volunteers, using known positive controls in a well established model, gatifloxacin was found to be no more phototoxic than placebo, and less so than ciprofloxacin and lomefloxacin.

A form of hemolytic uremic syndrome (HUS) has been associated with a few members of this class of molecules, including temafloxacin. A thorough independent review of the gatifloxacin safety database did not detect any case with clinical or laboratory findings suggestive of HUS.

Preclinical data in juvenile animals suggest that fluoroquinolone antibiotics may have a potential for causing tendon and joint abnormalities. A thorough review of the clinical safety database, which included only adults, found a single event of a torn tendon in a member of a comparator group and none among patients treated with gatifloxacin. Wording in the Pediatric Use subsection of the PRECAUTIONS section of the approved label contains the following drug class labeling, "Quinolones, including gatifloxacin, cause arthropathy and osteochondrotoxicity in juvenile animals (rats and dogs)."

Hypoglycemia has been associated with other products from this drug class. Based on evaluation of glucose homeostasis in normal volunteers and examination of the clinical safety database, hypoglycemia appears to be, at worst, a rare event not clearly associated with gatifloxacin. Special precautions to minimize these rare events do not appear warranted.

Safety was also evaluated by gender, race, and age. Among normal healthy volunteers, dizziness was reported more frequently in women than in men. This observation was not

confirmed in the larger population of gatifloxacin-treated patients in the clinical database. No other notable differences were identified.

Some fluoroquinolones have been associated with prolongation of the QTc interval, and rare malignant arrhythmia, namely torsades de pointes. The mechanism of the QTc effect of these drugs is not fully understood but may be related, in part, to inhibition of the rapidly activating delayed-rectifier potassium channel (IKr) in the heart. As noted in the Integrated Safety Review, a measurable relationship was found between plasma concentrations of gatifloxacin and prolongation of QTc, in volunteer studies assessing oral and intravenous doses ranging from 200 to 800 mg, where 55 subjects had 76 paired valid ECGs. No cardiovascular mortality or morbidity attributable to QTc prolongation occurred with gatifloxacin treatment in over 4000 subjects in the NDA, including 118 patients concurrently receiving drugs known to prolong the QTc interval and 139 patients with uncorrected hypokalemia. However, these numbers are too small to exclude a very limited risk of serious and life-threatening arrhythmia, that would be unacceptable, if this product were used for more than a single dose in a large number of patients with less serious infections, such as uncomplicated skin and skin structure infections.

RISK MANAGEMENT CONSIDERATIONS

Minimization of the potential risks have been addressed by wording in the WARNINGS, and PRECAUTIONS sections of the proposed package insert. In particular, a strong warning has been included which advises against the use of this drug in patients who may be at a particular high risk for prolongation of the QTc interval. In order to facilitate the communication of important safety information to the patient, a section entitled "Patient information About: TEQUIN™ (gatifloxacin) 200mg and 400mg Tablets" has been included at the end of the approved package insert.

WAIVER OF REQUIREMENT FOR PEDIATRIC STUDIES

The applicant has requested a waiver from the requirement to conduct pediatric studies for these NDAs. The safety and effectiveness of gatifloxacin in pediatric patients, adolescents (less than 18 years of age) have not been established. Although it is expected that the diseases represented in the approved indications for adults are similar to those in children and would respond in a similar fashion to treatment with gatifloxacin, there is a unique concern over potential joint abnormalities associated with the use of fluoroquinolone antibiotics in children. Thus, the potential risks in this population outweigh the potential benefits. Wording in the Pediatric Use subsection of the PRECAUTIONS section of the approved label contains the following drug class labeling, "Quinolones, including gatifloxacin, cause arthropathy and osteochondrotoxicity in juvenile animals (rats and dogs)." Therefore, under 21 CFR §314.55(c)(2)(i) a full waiver from the conduct of pediatric studies has been granted for these NDAs.

PHASE 4 COMMITMENTS

There is a need to evaluate and exclude the risk of rarer serious adverse events that would be unacceptable when gatifloxacin is used for uncomplicated infections in a large number of subjects. During a telephone conference with the applicant on December 16, 1999, and in subsequent correspondence to the FDA, the applicant committed to collect and submit post-marketing data confirming the safety of gatifloxacin, and thereby demonstrating an acceptable risk/benefit profile in the treatment of uncomplicated skin and skin structure infections. These data should come from a variety of sources, including but not limited to, clinical studies further evaluating the effect of gatifloxacin on QTc, as well as active and passive surveillance programs, that were detailed in the approval letter, dated December 17, 1999.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Division Director Memorandum

TO: NDA 21-085

FROM: Mark J Goldberger, M.D., MPH *MJL*

RE: Tequin® (gatifloxacin) Tablets, NDA 21-061
Tequin® (gatifloxacin) IV, NDA 21-062

DATE: Dec 17, 1999

Efficacy:

I agree with the overall assessment of the review team including that expressed by Dr. Cavaille-Coll in his Team Leader Memo. Gatifloxacin should prove to be a useful addition in the treatment of a number of infections particularly those of the respiratory tract. Based upon *in vitro* data, gatifloxacin has the potential to show enhanced activity against resistant gram + organisms, particularly PRSP. However, At present, Bristol Myers Squibb (BMS) has not submitted sufficient information to allow statements regarding such activity to be included in the "Indications and Usage" section of the product label. The ultimate usefulness of this drug will depend upon BMS performing additional clinical trials to assess the drug's activity in such settings. The absence of cytochrome 3A4 interactions and the lack of hepatic metabolism are advantages particularly in the setting of once daily dosing

Safety:

The relationship between exposure and Q-T prolongation with gatifloxacin is incompletely defined. Pre-clinical animal studies did not appear to show an effect. However, pharmacokinetic studies suggested a positive exposure response relationship. The company performed and submitted data from an *in vitro* model which suggested that the effect of gatifloxacin on the *I_{kr}* was not much different from ciprofloxacin and less than other approved flouroquinolones such as moxifloxacin, sparfloxacin and grepafloxacin. The information to allow an easy assessment of the clinical significance of quantitative changes in Q-T is not readily available for this as well as other products. We believe that the risk of serious clinical events with the degree of prolongation that we have seen with gatifloxacin, given the absence of pharmacokinetic interactions, the *I_{kr}* data and the limited clinical data, to be extremely low though not necessarily zero. We believe that through the combination of limiting indications, labeling which includes appropriate warnings and a patient information section and Phase IV commitments to obtain additional information, to be an appropriate approach to manage this risk.

It should be noted that during the review no concerns regarding the potential hepatotoxicity of this product were identified. This conclusion was supported by additional analyses beyond those originally included in the NDA that were performed by FDA reviewers or requested from the applicant.

Prior to the submission of the NDA and during the review there were cases of a hypersensitivity (anaphylactoid) reaction identified. These were observed during IV infusion in a dose escalation trial and in a few patients receiving PO therapy, primarily those with a diagnosis of sinusitis. Similar reactions have been reported with ciprofloxacin. We do not believe that these events are of sufficient severity to produce a significant health risk.

Both this issue and that of the Q-T prolongation are well covered in Dr. Korvick's safety review.

Postmarket requirements:

As noted earlier, we believe that both withholding the skin indication and requiring the agreed upon Phase IV commitments, have improved the risk benefit for approval of this product. Although uncomplicated UTI has many alternative therapies approved for treatment we believe that the risk for either a single dose regimen or for a three-day regimen at reduced (200mg) dose is very low. This also applies to the approval of single dose Rx for uncomplicated GC. The additional studies that BMS will perform as part of their Phase IV commitments will provide the opportunity to gain additional information about the safety profile of gatifloxacin particularly with regards to its effect on Q-T prolongation and to better understand the relationship between Q-T prolongation and likely clinical effects.

Pediatric Development:

Pediatric studies were not part of the NDA submission and the applicant has requested a waiver for pediatric studies even though they have an active development program underway. This program includes pharmacokinetic and single dose studies that include measurement of middle ear antimicrobial levels and plans for clinical trials in both complicated otitis and bacterial meningitis. Given the concerns about PRSP in these situations, clinical trials would be of considerable value. The Division and BMS are currently discussing the staging of these clinical trials and the amount of post-marketing safety information that should be available to support pediatric development.

**APPEARS THIS WAY
ON ORIGINAL**



410-590 AMMS
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Special Pathogens
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: August 8, 1997

TO: Douglas C. Kriesel, Ph.D., Director
Worldwide Regulatory Affairs
Ph: 203-284-6883
Fx: 203-284-7630

ADDRESS: Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

FROM: Brenda J. Atkins, Project Manager

THROUGH: Marianne Mann, M.D., Medical Officer
Joyce Korvick, M.D., Acting Team Leader

/S/

8-8-97

IND:

[Redacted]

8-8-97

SUBJECT: Questions for consideration by the FDA contained in the background package for the August 15, 1997, end-of-phase 2 meeting

A preliminary review of the five questions you wish the FDA to address for the pre-NDA meeting scheduled for August 15, 1997, has been performed. In order to facilitate this meeting, we have the following comments and concerns.

Question 1. Is the clinical plan outlined adequate to support the seven target indications?

Response:

Your phase II/III study of "Gatifloxacin in Patients with Uncomplicated Gonococcal Infection" (A1420-012) states that "an observed eradication rate of 95% is desirable for this indication" and also states that "the response rate for at least one gatifloxacin dose (should be) no more than 10% less than the rate for ofloxacin."

FDA requires a 95% observed eradication rate in the study drug treatment arm for this indication. As per the FDA Guidance Document: "Bacterial eradication should be the primary endpoint and at least 95% eradication should be expected." This is inconsistent with your protocol summary as above. Please address this inconsistency.

Question 2. Is the serologic testing proposed in protocols -002, -006, -037, and -038 adequate for identification of atypical pathogens?

Response:

Please clarify what laboratories will be performing the serologic tests for atypical pathogens and what testing kits will be used. Please also clarify the precise IgG and IgM titre cutoffs which will be considered diagnostic, since the current protocols do not define this clearly.

Additional testing (with cultures, and other technologies) may enhance your ability to detect infection with these atypical pathogens. Using serologic testing alone may result in a limited detection of cases, and may not provide enough documented infections to support an indication for these pathogens.

Question 3. For each indication, are the criteria for clinical cure adequate?

Response:

Dr. Mann has reviewed protocols -003, -006, and -002 for community acquired pneumonia and protocol -005 for uncomplicated skin and soft tissue infections and has conveyed comments for these indications to you. The criteria for clinical cure were adequate for these indications and protocols.

Dr. Mann will continue reviewing the protocols for each indication, and will be relating comments regarding the adequacy of study design (and criteria for clinical cure) for each remaining indication.

Question 4. Bioavailability of oral and intravenous gatifloxacin with similar indications for both products:

Response:

We will discuss this in greater detail with you at the 8/15/97 meeting. In general, however, we find the proposal acceptable. It is important that we have an adequate safety data base for the IV formulation, and that the labeled indications for the IV formulation be identical in nature (i.e for mild to moderate infections) to those for the PO formulation.

Question 5. PET scanning.

Response:

Please provide a more clear example of what type of labeling claims would be proposed from the PET studies. Please also provide additional information supporting and validating the use of PET scanning as a scientific technique to support these claims.

THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. If you have any additional questions regarding the contents of this facsimile, please contact me on (301) 827-2335.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Special Pathogens
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE CONFERENCE

DATE OF MEETING: September 19, 1997

IND: [REDACTED]

Drug: Oral Gatifloxacin

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute

Subject: Gonococcal and Urinary Tract Infection (UTI) Protocols

Meeting Chair: Marianne Mann, M.D.
Sponsor Chair: Douglas C. Kriesel, Ph.D.
Project Manager: Brenda Atkins

FDA Attendees, Titles, and Offices:

Teresa Wu, M.D., Acting Clinical Team Leader
Marianne Mann, M.D., Medical Officer
Nancy Silliman, Ph.D., Statistician
Brenda Atkins, Project Manager

External Constituent and Titles:

Claude Nicaise, M.D., Project Team Leader, Infectious Diseases Clinical Research
Janis Grechko, Ph.D., Director, Biostatistics and Data Management
Dennis Grasela, Pharm.D., Ph.D., Human Pharmacology
Todd Baumgarten, M.D., Clinical Monitor
Beth Stanton, Clinical Scientist
Joan Milsaps, Clinical Scientist
Robert Francis, Biostatistician
Joanna Yang, Biostatistician
Douglas Kriesel, Ph.D., Worldwide Regulatory Affairs (Liaison)

Background:

Bristol-Myers Squibb Pharmaceuticals (BMS) submitted multiple protocols under [REDACTED]. The purpose of this telecon was to convey FDA comments on a gonococcal protocol entitled, "A Randomized, Double-Blind, Multicenter, Phase III Study of Two Single Dose Regimens of Gatifloxacin and a Single Dose of Ofloxacin in the Treatment of Uncomplicated Gonococcal Infection", and three UTI protocols entitled "A Randomized, Double-Blind, Multicenter, Phase II/III Comparison of Two Doses of Gatifloxacin in the Treatment of Women with Acute Uncomplicated Urinary Tract Infection", "A Randomized, Double-Blind, Multicenter, Phase II/III Comparison of Two Doses of Gatifloxacin to Ciprofloxacin in the Treatment of Complicated

Urinary Tract Infection and Pyelonephritis", and A Randomized, Double-Blind, Multicenter, Phase II/III Comparison of Two Doses of Gatifloxacin to Ciprofloxacin in the Treatment of Complicated Urinary Tract Infection and Pyelonephritis". Additional issues were also discussed and the details of those issues are discussed under the "Additional agreements reached" section of this document. Facsimiles dated September 10 and September 12 documented FDA's comments prior to the telecon of September 19, 1997.

Objectives:

To provide the IND sponsor with FDA comments regarding the protocols submitted under IND [] listed above.

Treatment of Uncomplicated Gonococcal Infection Protocol:

Discussion Item 1: Rates of eradication

Discussion:

The proposed trial needs to demonstrate at least 95% bacterial eradication in the gatifloxacin arm(s) (for each gender) in order to support a claim for gonococcal cervicitis and gonococcal urethritis. The protocol describes a primary efficacy analysis which will compare each gatifloxacin dose to ofloxacin, but does not describe these absolute rates of eradication which are required for these indications. While this was agreed upon in our August 15, 1997, end-of-phase 2 meeting with you, it is recommended that you submit an amendment to the IND addressing this issue.

Action Item:

The sponsor agreed and will include this information in the detailed analysis plan to be submitted soon.

Discussion Item 2: Labeling

Discussion:

To support wording in the label for beta-lactamase producing organisms, at least 95% eradication should be demonstrated in at least 40 patients (20 men and 20 women) as a subset analysis.

Action Item:

No action necessary. The sponsor noted this.

Discussion Item 3: Establishing effectiveness

Discussion:

Effectiveness in uncomplicated gonococcal urethritis/cervicitis should be established in at least 100 evaluable men and 100 evaluable women. Once this has been established, effectiveness in gonococcal pharyngitis or proctitis may be evaluated. A minimum of 20 patients of each gender for each additional body site (i.e., rectum, pharynx) where at least 90% bacterial eradication is demonstrated is sufficient to establish effectiveness in these additional infections.

Action Item:

No action necessary. The sponsor noted this.

Discussion Item 4: Concurrent infections

Discussion:

Many patients with gonorrhea may have concurrent infections (chlamydia, syphilis). If these are detected, treatment of these other sexually transmitted diseases may be started after the post-treatment cultures have been taken to assess eradication of *Neisseria gonorrhoeae*. Alternatively, if the investigator feels it is in the patient's best interest, these patients may be excluded from the study. The protocol should address the management of these patients in greater detail.

Action Item:

The sponsor agreed to amend protocol A1420-012 to include clarification about how patients with concomitant sexually transmitted diseases (such as chlamydia or syphilis), if detected, will be managed in regards to study enrollment. (E.g. Will such patients be enrolled? If so, will treatment be deferred? Etc.) Specific treatment outlines of concomitant STDs is not necessary, however. In addition, the sponsor noted that they will be submitting a sub-protocol to be performed at two centers, in which eradication of chlamydia organisms will be evaluated. It was stressed by FDA that this sub-study would be considered a phase I/II study and would not be sufficient to support a chlamydia indication.

Discussion Item 5: Construction of confidence intervals

Discussion:

Please clarify exactly how confidence intervals are to be constructed (e.g., center-adjusted, normal approximation to the binomial incorporating the continuity correction, etc.).

Action Item:

Randomization in this trial is stratified by both center and gender. This is to insure adequate representation of both treatment regimens at each center, and also to insure that the sponsor is able to meet regulatory requirements about adequate numbers of patients in each gender. Since the sponsor does not feel that response will differ by center or gender, confidence intervals will not adjust for either factor. This will be detailed in the analysis plan that the sponsor intends to submit sometime in the future.

Discussion Item 6: Examining evaluability

Discussion:

Page 14 of this protocol states that "the study will close when 100 evaluable subjects per gender have been accrued." This implies that evaluability is to be examined for individual patients while the trial is still ongoing. As the objective is to enroll 100 evaluable subjects per gender for each of the ciprofloxacin arms, but only 50 evaluable subjects per gender for the ofloxacin arm, it appears that the process of examining evaluability could potentially unblind the trial (at least to you). Please clarify whether blinding will, in fact, be compromised?

Action Item:

Evaluability rates will be assessed within gender, but pooled across all three treatment arms. As a result, blinding of the study will not be compromised.

Discussion Item 7: Adjusting and the number of multiple comparisons

Discussion:

You are adjusting for two multiple comparisons (each of the gatifloxacin arms versus the ofloxacin arm). Since the protocol states on page 10 that one of the objectives of the trial is to "assess safety and efficacy of these two doses of gatifloxacin relative to each other", it appears that you should actually be adjusting for three multiple comparisons.

Action Item:

The sponsor stated that they intended for only two primary comparisons to exist (each of the gatifloxacin arms versus the ofloxacin arm). The FDA statistician pointed out that if this trial is to be used to pick one of the gatifloxacin arms for marketing, then there are in fact three primary comparisons of interest (the previous two plus the comparison of the two gatifloxacin arms). The sponsor stated that they would check their power assuming they need to adjust for 3 primary comparisons and get back to us about how they plan to proceed.

Treatment of Women with Acute Uncomplicated Urinary Tract Infection Protocol:

Discussion Item 8: Rates of eradication

Discussion:

One of the two controlled clinical trials in support of ciprofloxacin revealed a marginally acceptable rate of bacterial eradication (*E. coli*) of 91%. In agreement, the bacteriologic eradication rate in the ciprofloxacin arm for this trial is estimated to be 90%. Be advised that if gatifloxacin has an absolute efficacy rate of bacteriologic eradication which is significantly below 90%, this may not support approval (even if the lower bound of the 90% confidence interval for the absolute difference between gatifloxacin and ciprofloxacin lies within 10%). This was discussed at the August 15, 1997, end-of-phase 2 meeting as well.

Action Item:

No action necessary. The sponsor agreed and noted that this was also discussed at the end-of-phase 2 meeting on August 15, 1997.

Discussion Item 9: Typographical error

Discussion:

Page 23 of the protocol contains a typographical error for the definition of Long-Term, Sustained Eradication. This definition currently states that a urine culture taken within the day +29 to +42 visit shows that all uropathogens found at entry at $\geq 10^5$ cfu/mL are reduced to $\geq 10^4$ cfu/mL. Presumably, the definition should instead state that a urine culture taken within the day +29 to +42 visit shows that all uropathogens found at entry at $\geq 10^5$ cfu/mL are reduced to $< 10^4$ cfu/mL.

Action Item:

No action necessary. The sponsor noted this typographical error.

Discussion Item 10: Bacteriologic and clinical outcome of "Unable to Determine"

Discussion:

The bacteriologic and clinical outcome of "Unable to Determine" is missing from this protocol. Please clarify how patients who are lost to follow-up or who receive systemic antibiotics with activity against the uropathogen(s) for a reason other than UTI during the study will be classified.

Action Item:

The sponsor noted this omission of "Unable to Determine" from the protocol and will submit an amended protocol.

Discussion Item 11: Construction of confidence intervals.

Discussion:

Please clarify exactly how confidence intervals are to be constructed (e.g., center-adjusted, normal approximation to the binomial incorporating the continuity correction, etc.).

Action Item:

The randomization in this trial is stratified by site to allow for adequate representation of each treatment arm at each center. Since the sponsor does not expect treatment response to differ across centers, any confidence intervals produced will not adjust for center. Confidence intervals are to be computed using the exact method. An analysis plan that outlines this approach will be submitted in the future.

Treatment of Complicated Urinary Tract Infection and Pyelonephritis Protocol:

Discussion Item 12: Support for a pyelonephritis indication

Discussion:

In order to support a pyelonephritis indication, a minimum of 30 patients per treatment arm with this condition are recommended.

Action Item:

No action necessary. It was agreed that 30 gatifloxacin and 30 comparator patients (from studies AI420-011 and AI420-031 combined) would be acceptable.

Discussion Item 13: Inclusion criteria to support pyelonephritis indication

Discussion:

The guidance document recommends that inclusion criteria for both pyelonephritis and complicated urinary tract infection should include patients with clinical evidence of fever, chills, and flank pain. The submitted protocols require fever and flank pain, but allow for either the presence or absence of chills. This is acceptable, although not in direct agreement with the guidance document.

Action Item:

No action necessary. The sponsor agreed.

Discussion Item 14: Entry criteria for complicated UTI patients

Discussion:

The entry criteria for complicated UTI require that patients:

•have one or more of the following: dysuria, urgency, frequency, suprapubic pain, flank pain, fever ($> 38.0^{\circ}\text{C}$) with or without chills, or costovertebral angle tenderness.

It is recommended that this criteria be revised to include patients who:

•have fever ($> 38.0^{\circ}\text{C}$) with or without chills and have one or more of the following: dysuria, urgency, frequency, suprapubic pain, flank pain, or costovertebral angle tenderness.

Action Item:

No action necessary. The FDA agreed with the sponsor's criterion for complicated UTI which was consistent with IDSA guidelines.

Discussion Item 15: Construction of confidence intervals

Discussion:

For each of the two protocols, please clarify exactly how confidence intervals are to be constructed (e.g., center-adjusted, normal approximation to the binomial incorporating the continuity correction, etc.).

Action Item:

Randomization in both protocols is stratified by pyelonephritis status (yes, no) and center. The sponsor does expect treatment response to differ by pyelonephritis status, and will use the DerSimonian and Laird method of accounting for this covariate (pyelonephritis status) in the construction of confidence intervals. An analysis plan that outlines this approach will be submitted in the future.

Additional agreements reached:

1. The sponsor agreed to assessing the clinical evaluability of patients in the sinusitis protocol (protocol A1420-007) using a definition which includes those patients who received at least 80% of study drug. This would correspond to at least 8 days of treatment with gatifloxacin and 11 days of treatment of clarithromycin.
2. FDA agreed to check on eligibility criteria for patients with uncomplicated UTI. Should this definition include patients with $\geq 10^5$ cfu/mL, or $\geq 10^3$ cfu/mL? (Note: FDA responded via facsimile dated 9/26/97.)
3. FDA agreed that the sponsor could study patients ≥ 16 years of age as long as it was understood that this data would not support a pediatric indication. The sponsor agreed.
4. The sponsor asked if the comparison arm of IV Ceftriaxone \pm Erythromycin followed by po Clarithromycin was acceptable for the community-acquired pneumonia study A1420-037. FDA agreed that this arm was acceptable. Additional comments regarding the IV studies for community acquired pneumonia will be addressed in an upcoming teleconference to be scheduled.

5. The sponsor related that safety results from the 200 mg IV dosing cohort in the PK study will be available next week. It was agreed that the sponsor will fax these results to FDA on September 25, 1997, and that FDA would attempt to respond with a teleconference either September 25, 1997 or September 26, 1997 to address these results. The sponsor agreed with this plan.

Signature, minutes preparer: /S/ Date: 9/26/97
Conference Chair (or designated signatory) /S/ Date 9/29/97

CC:

Division file

HFD-590/ActgTL/TWu.

HFD-590/MO/MMann

HFD-725/STAT/NSilliman

HFD-590/CSO/BAtkins

Record of Telephone Conference

Address:

Request date: 09/10/97 verbal by FDA

Confirmation date: 09/10/97 facsimile

Fax date: 09/10/97 (Clin)/09/12/97 (Stat)

Meeting date: 09/19/97

Draft completed date: 09/26/97

Minutes finalized:

Letter drafted: none

Letter stamp date: none



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Special Pathogens
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

RECORD OF INDUSTRY MEETING

Meeting Date: October 7, 1997 Time: 1:00 Location: S400

IND Numbers and Drug Name: Gatifloxacin for Oral Use
 Gatifloxacin for Intravenous Use

External meeting requestor: Bristol-Myers Squibb Company

Type of Meeting: End-of-phase 2 meeting

Meeting Chair: Norman Schmuff, Ph.D. Sponsor Chair: Satyam Upadrashta, Ph.D.

Meeting Recorder: Brenda J. Atkins, Project Manager

FDA Attendees. Titles, and Offices:

Norman Schmuff, Ph.D., Chemistry Team Leader, DSPIDP
Gene Holbert, Ph.D., Chemist Reviewer, DSPIDP
Chi-Wan Chen, Ph.D., Division Director, Division of New Drug Chemistry III
Brenda J. Atkins, Project Manager, DSPIDP

External Constituent and Titles:

A. Agharkar, Ph.D., Executive Director, Pharmaceuticals R&D
R. Corrao, Senior Research Scientist, Pharmaceuticals R&D
F. Mayerl, Ph.D., Senior CMC Documentation Scientist, R&D
M. Miyashita, Ph.D., Manager, Organic Syntheses, Kyorin Pharmaceutical Co., Ltd.,
Japan
K. Niimura, Senior Tech. Staff, Pharmaceutic Research, Kyorin Pharmaceutical Co.,
Ltd., Japan
Ti Lento, Interpreter
K. Raghavan, Ph.D., Senior Research Investigator, Pharmaceuticals R&D
E. Sato, Associate Director, QA, Kyorin Pharmaceutical Co., Ltd., Japan
L. Sechler, Ph.D., Senior Research Investigator, Pharmaceuticals R&D
P. Shah, Ph.D., Group Leader, Analytical R&D
R. Simon, Executive Director, Worldwide Regulatory Affairs
Michael Burnett, Director, Worldwide Regulatory Affairs (CMC)
Satyam Upadrashta, Manager, Worldwide Regulatory Affairs

Background:

On August 4, 1997, the sponsor requested a face-to-face end of phase 2 meeting with FDA representatives in the Division of Special Pathogens and Immunologic Drug Products to

7. The ready to use premix IV flexible bags are currently being used commercially by Abbott Laboratories for other products. Due to drug substance photosensitivity, the observed effects seen in the gatifloxacin IV formulation are a decrease in potency and a slight discoloration. The decrease in potency is not attributable to an increase in the level of any single impurity.
8. Sterility testing for the IV formulation will be done only at the zero-time and at the end-time points at one station, i.e., 25 degrees C only. The FDA advised the sponsor that pyrogen challenge test should be added at some intermediate intervals.
9. The sponsor was advised that parametric release regarding sterility testing is not generally recommended for the IV drug product; however, if the sponsor is intent on pursuing this issue, Peter J. Cooney, Ph.D., Supervisory Microbiologist, should be contacted.
10. Qualification of extractables will be part of the sponsor's development plan and data will be provided to the FDA regarding the IV drug product.

Unresolved issues or issues requiring further discussion:

1. None

Decisions (agreements reached):

1. The sponsor will present the DMFs in a U.S. format.
2. The proposed stability protocols for the oral dosage form, IV dosage form, and the ready-to-use IV flexible bags to support filing the NDAs are adequate.
3. The 9-month stability data at the time of NDA filing for the pre-mix flexible bag presentation is acceptable with the FDA; however 12-month stability data should be provided when available.
4. The sponsor will inform the FDA regarding its decision in setting up a specification for the pentahydrate found in the solid-state forms of gatifloxacin.
5. Abbott's DMF on bag technology will be made available to the FDA to support the NDA filing.
6. The sponsor agreed to provide data regarding qualification of extractables.

Signature, minutes preparer:

Concurrence Chair:

/S/ */S/* *1/30/98* */S/*
/S/ *1/30/98* */S/*

Attachments/Handouts



590 ATKINS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Special Pathogens
and Immunologic Drug Products
Food and Drug Administration
Rockville MD 20857

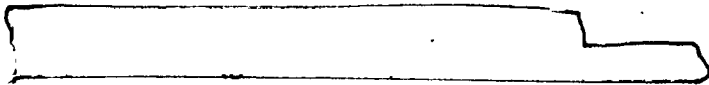
MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

DATE: November 14, 1997


TO: Douglas C. Kriesel, Ph.D., Director
Worldwide Regulatory Affairs
Ph: 203-284-6883
Fx: 203-284-7630

ADDRESS: Bristol-Myers Squibb (BMS) Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

FROM: Brenda J. Atkins, Project Manager *B. Atkins*

IND: 

SUBJECT: Agreements reached during the October 31, and November 6, 1997,
discussions relating to Protocol A1420-032

Reference is made to your IND submission  dated October 3, 1997, containing a protocol no. A1420-032 entitled "Randomized, Double-Blind, Placebo-Controlled Comparison of the Effects of Multiple Dose Gatifloxacin or Ciprofloxacin on Glucose Homeostasis and Insulin Production/Secretion in Type II Diabetics Maintained with Diet and Exercise".

The purpose of this facsimile is to provide in writing the following agreements made between FDA and BMS during the subject meeting dates. Agreements reached were as follows.

1. This protocol evaluates the effect of gatifloxacin on glucose control in very mild diabetics who are controlled with diet and exercise. It does not address the effect of gatifloxacin on the much larger population of diabetic patients who require medical therapy. The protocol is safe, but the criteria for subject-discontinuation which currently include only symptomatic hypo or hyperglycemia should be revised to also include objective serum glucose level cutoffs. Serum glucose levels below 50 or exceeding 300 mg/dl are suggested.

This issue was discussed in an October 31, 1997, teleconference with BMS representatives. It was noted by BMS that they do intend to study diabetics who are taking oral hypoglycemics in a forthcoming protocol. BMS agreed with serum glucose cutoff levels, as long as they are shown in two or more repeated measurements. FDA agreed with this approach.

2. The second issue of concern following the October 31, 1997, teleconference was the selection of the 90% confidence interval for the primary endpoint of AUC following glucose tolerance testing. BMS chose a relatively wide 90% confidence interval (CI) of 0.67 to 1.50 as defining no effect, and the FDA had concerns about this, particularly since this is a safety endpoint. It was agreed in a followup teleconference on November 6, 1997, that the study could proceed as planned since narrowing the CI would greatly increase the need to enroll more patients and would make the study unfeasible. It was also agreed that defining a 90% confidence interval for "no effect" on glucose tolerance AUCs was very difficult, particularly given the high degree of inter-patient variability with this endpoint. FDA will evaluate the data provided by this study with the caveat that a 90% confidence defining "no effect" is not clear. Ultimately, the effect of gatifloxacin in diabetics will be most clearly demonstrated in the ongoing clinical trials of patients with a variety of infections.

THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. If you have any questions regarding the content of this facsimile, please contact Brenda Atkins, Project Manager, at (301) 827-2335.

**APPEARS THIS WAY
ON ORIGINAL**



MEMORANDUM OF TELEPHONE CONFERENCE

DATE OF MEETING: January 12, 1998

INDs:

Drugs: Oral and IV Gatifloxacin

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute

Subject: IV Gatifloxacin Protocol Involving Healthy Volunteers
and Oral Gatifloxacin Protocol for Uncomplicated Skin and
Soft Tissue Infections

Meeting Chair: Marianne Mann, M.D.
Sponsor Chair: Douglas C. Kriesel, Ph.D.
Project Manager: Brenda Atkins

FDA Attendees, Titles, and Offices:

Marianne Mann, M.D., Acting Medical Team Leader
Rigoberto Roca, M.D., Medical Officer
Brenda Atkins, Project Manager

External Constituents and Titles:

Claude Nicaise, M.D., Project Team Leader, Infectious Diseases Clinical Research
Jeanne Breen, M.D., Associate Director, Anti-Infective Diseases Clinical Research
Roger Echols, M.D., Vice-President, Anti-Infective Diseases Clinical Research
Dennis Grasela, Pharm.D., Ph.D., Associate Director, Human Pharmacology
Randall Soltys, Ph.D., Director, Toxicology
Howard Mayer, M.D., Associate Director, Anti-Infective Diseases Clinical Research
Maria Palmisano, M.D., Allergist, Princeton University
Douglas Kriesel, Ph.D., Worldwide Regulatory Affairs (Liaison)

Background:

Bristol-Myers Squibb Pharmaceuticals (BMS) submitted in response to a November 25, 1997, teleconference and to facsimiles dated December 2 and 4, 1997, under submission number 013, a report entitled "Local Reactions to Intravenous Study Drug Administration" which included an overview and (1) relevant non-clinical safety data, (2) blinded safety data from all cohorts in the Phase 1 IV study (AI420-025), (3) a summary of selected safety information from the Phase 2 gatifloxacin trials using the tablet formulation, and (4) a literature review of intravenous fluoroquinolone-induced local IV site reactions. This submission also contained blinded safety information from patients on IV therapy in the Phase 3 pneumonia studies (AI420-C37 and AI420-038).

A FDA facsimile dated January 9, 1998, raised additional concerns pertaining to protocol AI420-005 entitled "A Randomized, Double Blind, Multicenter, Comparative Study of Gatifloxacin Versus Levofloxacin in the Treatment of Uncomplicated Skin and Soft Tissue Infections", and introduced the reviewing medical officer, Dr. Rigoberto Roca, as the assigned reviewer to review that portion of the NDA submission.

Objectives:

To discuss the contents of IV Gatifloxacin [redacted] and outstanding concerns pertaining to protocol AI420-005 under [redacted]

IV Gatifloxacin

Discussion:

1. BMS asked if the unblinded safety data could be submitted in 4 to 6 months instead of next month (February 1998).
2. Dr. Mann commended BMS on the excellent job done in the conduct of protocol AI420-025. BMS was informed that protocols AI420-037 and AI420-038 for community acquired pneumonia (CAP) could proceed.
3. Because a significant number of subjects experienced local skin reactions at the infusion site, Dr. Mann requested that BMS conduct tests to better support histamine release levels of IV gatifloxacin. She suggested that this could be done as an in vitro study by testing basophils or as an ex vivo study by collecting skin samples at the injection site of IV gatifloxacin subjects. In vivo studies to measure histamine release are unreliable because measurement of circulating histamine levels is difficult. It was emphasized to BMS that the more supportive data obtained on this matter, the better.
4. The IV gatifloxacin formulation was changed because of some hint of precipitation was observed in one or two vials in one batch. The formulation for the CAPs protocols is the new formulation containing dextrose. The pharmacokinetic study was done with the old formulation containing saline.
5. Ninety-two patients are currently enrolled in the CAPs protocols. As of January 5, 1998, one half of the 66 patients presumably on IV gatifloxacin have not experienced any serious adverse events including local reactions.

Uncomplicated Skin and Soft Tissue Infections

6. BMS was advised that if the occurrence of Achilles' heel and other tendon ruptures are occurring in patients on gatifloxacin that a revised protocol would be requested by the FDA to address this issue. BMS reported that currently, 1,500 people have taken gatifloxacin and this adverse event has not been reported.

7. BMS will discuss internally how to better document the test of cure and will be getting back with the FDA in the very near future. To date, 250 patients have been enrolled and a total of 430 patients are targeted for protocol A1420-005. Analytical plans for the phase 3 studies have not been finalized but should be completed in the near future.
8. BMS stated that frequent and open communications will continue with investigators to assure compliance under the specimen and transport section of the protocol describing the methods for collecting cultures.

Action/Outcome:

1. The FDA agreed to wait 4 to 6 months (closer to 4 months) for the unblinded safety data for protocol A1420-025.
2. In reference to IV gatifloxacin, BMS was informed that the FDA will be looking closely at the frequency with which local skin reactions are experienced by subjects at the infusion site.
3. BMS will provide any and all additional data on the 30 year old male subject who experienced an anaphylactic like reaction as soon as possible. According to BMS, the subject had no previous history of asthma and there was no prior quinolone exposure.
4. BMS will revisit the evaluability criteria for bacteriologic response in protocol A1420-005 and develop a better method of reporting test of cure data to the FDA.

concurrency:

HFD-590/ActingTL/MMann

HFD-590/MO/RRoca,

HFD-590/CSO/BATkins/drafted 012098

CC:

Division file

HFD-590/ActingTL/MMann

HFD-590/MO/RRoca

HFD-520/PHARM/AEllis

HFD-590/MiCRO/PDionne

HFD-880/BIOPHARM/PColangelo

HFD-590/CHEM/GHolbert

HFD-590/STAT/NSilliman

HFD-590/CSO/BATkins/drafted01/20/98

Record of Telephone Conference

Address: